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Controlled Temperature Tissue Fusion: Argon Laser Welding of Canine Intestine In Vitro

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Background and Objective: **Thermal denaturation of proteins is recognized as a rate process governed by the local temperature-time response and is believed to be the principal mechanism for photothermal tissue welding. Since rate processes are exponential with temperature, feedback control of tissue surface temperature is hypothesized to create a quasi-constant rate of denaturation that will enhance the tissue welding process.**
Study Design, Materials and Methods: **Controlled temperature tissue welding of severed edges of fresh canine jejunum was performed in vitro by remote sensing of tissue surface temperature with an infrared sensor. A hardware controlled temperature feedback system opened and closed a shutter located in the beam path of an argon ion laser to provide constant temperature welding.**
Results: **Strong tissue fusion was not possible at or below a surface temperature of 70°C, but was accomplished at 80°, 90°, 95°, and 100°C. Fusion was achieved with thermal coagulation of the collagenous submucosa and mucosal tissues. The bursting strength of welds created at 90°C and 95°C were significantly stronger than those performed at 80°C.**
Conclusion: **Laser-assisted intestinal anastomoses created in vitro are optimally strong at 90–95°C feedback control temperatures.**

Key words: argon laser, dosimetry, feedback control, intestine, jejunum, quasi-constant temperature control, temperature feedback, tissue fusion, tissue welding

INTRODUCTION

Laser-assisted tissue welding (LTW) has been investigated as an additional surgical tool to improve the anastomosis of several blood vessels, nerves, and a variety of hollow organs. LTW can provide: (1) immediate fluid-tight sealing, (2) reduce foreign body reaction associated with healing around sutures, (3) preserve the mechanical integrity of the "weld" site, and (4) achieve successful anastomosis rates comparable to conventional suture techniques [1–3]. However, extensive training is required to form reproducibly successful bonds. The lack of satisfactory objective criteria for optimal laser exposure parameters required to produce an immediately durable weld has long been regarded as a major limitation of LTW [1,4–8].

Absorption of laser light results in the generation of a distributive heat source in tissue. If sufficient laser energy is deposited, tissue components are thermally denatured. The thermal de-

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naturation of proteins is believed to be the principal mechanism for heat-mediated welding and sealing of ruptured organs [5,6,9,10]. Experience has shown that excessive irradiation may result in more thermal damage than needed for the "laser-induced" bond, whereas inadequate heat deposition results in tissue dehydration without effective fusion [1,4,6].

Temporal profiles of tissue temperature depend not only on irradiation parameters but also the optical and thermal properties of tissue being irradiated. These properties are not constant and may quickly and dramatically change during laser irradiation [10–13]. Dehydration lowers thermal conductivity [14–17], which decreases heat diffusion and in turn tends drastically to increase local temperatures. In addition, light scattering is increased and often absorption is slightly decreased as a consequence of thermal damage [18–22]. As tissue dehydrates, laser-induced temperatures may exceed 100°C before a surgeon can respond to visual changes of the tissue.

Ideally, automated dosimetry should be based upon indicators of thermal damage during laser irradiation. In this report, we hypothesize that tissue surface temperature is an indicator of tissue status during LTW. We recognize that denaturation is a rate process governed by the local temperature-time response [23,24]. However, since rate processes are exponential with temperature and linear with time, we believe feedback control of tissue surface temperature within a narrow margin will create a rather constant rate of denaturation. This will eliminate exponential increases in the rate of denaturation associated with excessive thermal insult, i.e., rapidly increasing temperatures. Data is presented on the effectiveness of quasi-constant temperature control of laser-assisted welds of severed canine jejunum at temperatures from 80–100°C performed in vitro. We used different feedback control temperatures (FCT) to investigate the effectiveness of different denaturation rate reactions and the importance of the magnitude of temperature in the welding process.

Although temperature control is believed to produce a constant rate reaction, it does not provide an end point for terminating laser irradiation. Currently, completion of welds requires a decision based upon visual observation, i.e., whitening, of the tissue. We hypothesize that by gating laser irradiation to control tissue surface temperature within a narrow margin, the welding process is enhanced. This hypothesis is tested by welding in vitro jejunal small intestinal segments with argon laser radiation under temperature feedback control.

MATERIALS AND METHODS

Surgical Procedures

Jejunal small intestinal segments were harvested within 20 minutes of euthanasia from seven mongrel dogs weighing 20–25 kg. The segments were flushed with phosphate-buffered isotonic saline (PBS) or Ringer's lactate to clean out the contents. The cleaned segments were placed in a beaker containing PBS and kept at room temperature until time of use. Segments were not placed in a refrigerator because intestinal tissue becomes very crisp and hard at cold temperatures, resulting in unsuccessful experiments or complications. One of the major difficulties we encountered working with harvested segments of the intestinal tract was their susceptibility/tendency to deteriorate rapidly. Segments that were not used within a maximum of 10–12 hours after harvest were discarded.

Uniform samples ~12 cm in length were mounted and secured with a suture tie on one end of a rigid rubber hose specifically modified to prevent slippage during bursting pressure measurements (see Fig. 1). Transmural transverse enterotomies (one per sample, 10–12 mm long) were created using a scalpel and fine scissors. The edges of the enterotomies were approximated using three 6-0 sutures placed 3–4 mm apart. All enterotomies were laser welded under temperature feedback control.

System Components

In our laboratory, a thermal feedback-controlled laser delivery system was developed that uses remote temperature sensing. The operation of the system is based on an on-off control algorithm implemented entirely in the hardware that utilizes thermal feedback from a calibrated Infra-Red (IR) sensor [25]. We have modified an existing IR sensor by inserting a dichroic beamsplitter in the optical path to incorporate laser delivery into the same housing. The improved design made the temperature sensor a more practical experimental device by using the same optics both for laser delivery and temperature detection, and thus by eliminating the need to focus temperature sensor and laser delivery separately before each experiment. The laser delivery efficiency, η, of the co-aligned device is 28%. The device is oriented

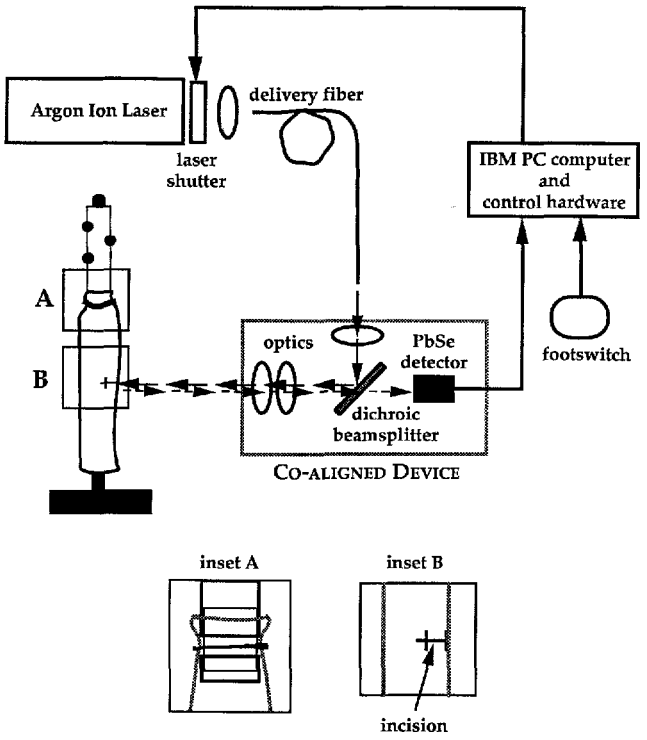

Fig. 1. Experimental setup for intestinal welding in vitro. The sample is placed in the focal plane of the co-aligned device and the laser beam is directed perpendicular to the weld site. The incision and the arrangement of sutures are shown in **A.** An indentation in the rubber hose prevents slippage of sample as shown in **B.**

horizontally and is stationary. The experimental setup of the controlled temperature laser delivery system is shown in Figure 1. Prior to welding, an anastomotic site is aligned to the focal plane of the device using a very low power beam directed perpendicularly to the enterotomy (see Fig. 1). Surface temperature signals are collected and recorded continuously at 200 millisecond intervals by an IBM PC computer from a 0.6 mm diameter field of view (FOV) at the center of the 2 mm diameter laser spot as the anastomotic side is moved through the irradiation field to ensure adequate laser exposure along the full length of the enterotomy. The IBM PC computer is used primarily to calibrate the sensor, generate a reference (control temperature) voltage for feedback control, and acquire temperature data at 200 Hz.

The temperature sensor is calibrated (range: 50–120°C) prior to welding by placing a black body reference source (COMO Research, Austin, TX) [26] in the focal plane of the co-aligned device. The heart of our temperature sensor is a 0.25 mm^2 thermoelectrically cooled photo-conductive lead-selenide (PbSe) detector (Infrared Industries, Orlando, FL) operating in the 3–5 μm IR band. A laser shutter (nm Laser SC-1100/LS200FNS, nm Laser, Sunnyvale, CA) is placed in the path of a continuous wave (cw) argon ion laser (Coherent, Innova 100, Palo Alto, CA) beam that operates at multi-line visible wavelengths (MLVS) from 488 to 515 nm. The laser shutter is under the control of the IBM PC computer and associated control hardware that are activated by a thermal feedback signal. Whenever the tissue surface temperature exceeds a preselected control value, the laser shutter is closed. The shutter is reopened when tissue temperature falls below the same preselected control value. Opening and closing the laser shutter regulates the average fluence rate of the argon ion laser beam and tissue surface temperature is maintained within a narrow band of temperatures throughout the welding procedure. The worst-case temperature resolution and response time of the system are ~1°C and ~45 msec, respectively.

The feedback control system is activated and laser irradiation begins when the foot switch is depressed. By keeping the foot switch depressed throughout an experiment, laser dosimetry is controlled entirely by temperature feedback.

Experimental Procedure

Intestinal welding was performed at 80°, 90°, 95°, and 100°C using temperature feedback control. Since blood is the main chromophore absorbing argon laser irradiation, one small piece of tissue from each jejunal segment was used to adjust laser power to reach the desired surface control temperature within the first 10–20 seconds irradiation of a single spot of 2 mm diameter. Depending on the amount of blood present in tissue, laser power was varied between 2.5–4 W resulting in an irradiance of 22–35 W/cm^2. The full length of the enterotomy was "brush-welded" by slowly and manually moving the specimen sideways. The tissue was irradiated until the apposed edges of the enterotomy fused, visually marked by whitening of the tissue. Irradiation of sutures was avoided as much as possible, but usually sutures were in the field of irradiation, and occasionally they were burned.

Following controlled temperature intestinal welding, the rubber hose was connected to a water-filled flask. The open end of the sample was clamped, the rubber hose was filled with water, the flask was sealed, and acute bursting/leaking pressures (BLPs) were measured. To measure the

bursting strength of the welded sample, a hand pump was used to pump air into the sealed flask and thus to pressurize the water. Samples were pressurized slowly at a steady rate of ~20 mmHg/sec or less. Pressure measurements were made close to the air/water interface. The pressure at which either a first drop of water escaped from a breaking section of the weld or the weld violently broke open were recorded as BLP of that weld. BLP tested samples were immediately immersed in buffered 10% formalin for fixation.

Histological Examination

Two tissue blocks representative of each weld were dehydrated in graded ethanol solutions and xylene and embedded in paraffin. The blocks were taken transverse to the welds and along the longitudinal axis of the bowel segment. Representative 4-μm-thick sections were examined with light and transmission polarizing microscopy. Because all specimens had been at least partially ruptured by the bursting/leaking pressure test prior to fixation, bond integrity was not evaluated. The location and extent of thermal damage including collagen hyalinization, collagen, and smooth muscle birefringence changes, tissue vacuolization (water vaporization), and carbonization were sought and measured. These quantitative and qualitative markers of thermal damage were compared to the irradiation parameters, tissue temperatures, and bursting pressures.

Data Analysis

Statistical analysis of BLP measurements were carried out using Microsoft Excel® 4.0. Data were plotted on KaleidaGraph™ 3.0.

RESULTS

Intestinal welding was performed in vitro at 80°C (n = 19), 90°C (n = 18), 95°C (n = 13), and 100°C (n = 5) feedback control temperatures (FCTs) on a total of 55 samples from seven dogs. Attempts were made initially to weld tissue at or below a surface temperature of 70°C, but all of those welds failed.

Depending on laser power and control temperature, the "exposure times" for laser-assisted tissue welding of 10–12-mm-long transverse enterotomies varied between 200–800 seconds. In this study, "exposure time" was defined as the total time that feedback control was in effect including laser-off times. After a learning period the average "exposure time" decreased, to average around 300–350 seconds (Fig. 2). In general, the laser beam was "on" for at least 50% of the total "exposure time" at 80°C FCT in "steady state." In other words, once surface temperature reached the preselected control value, the duty cycle of the laser irradiation was 50% and higher. For single spot irradiation on canine jejunal segments, the duty cycle increased when a higher control temperature was chosen. At 100°C FCT, the duty cycle for single spot irradiation was ~75%, and it took a longer time to reach the control value, 100°C, than 95°C or lower FCT. A comparative temperature time history of an intestinal welding experiment with and without temperature feedback control is given in Figure 3. Sharp decreases in temperature correspond to moving the tissue to an unheated or "cooled" region.

The BLPs of welded anastomoses are shown in Figure 4. We have observed that after a learning period, stronger welds were created at the same control temperatures. The bursting pressures of 80°C and 90°C temperature-controlled intestinal welds of specimens from the first three dogs were lower than similar intestinal welds of specimens from the following dogs. However, when the BLPs of intestinal welds were normalized with respect to the BLPs at 80°C, the lowest temperature at which controlled temperature welds were successfully formed, for each dog, the relationships of control temperature to BLP became significant (Fig. 5a). Overall, BLPs were directly proportional to the FCT (Fig. 5b). Weaker welds were created at 80°C FCT, whereas stronger welds were created at 90°C and 95°C FCTs. A limited number of experiments were carried out at 100°C FCT on dog number 7 to determine the effect of this temperature on bond strength.

A student's t-test applied to the normalized BLPs of welds at different FCTs revealed a statistically significant increase in BLPs of welds when FCT was raised from 80°C to 90–95°C ($P < 0.05$). There was no statistically significant difference between the BLPs of 90°C and 95°C welded specimens. Furthermore, from the limited number of experiments at 100°C control temperature, there was no statistically significant difference between 100°C over 80°, 90°, and 95°C specimens.

Histological examination revealed that serosa and muscularis propia (the outer thicker muscle of the gut) retracted in response to laser irradiation. Since most of the bonds had split during the BLP testing, few intact bonds were available for analysis. In those sections, including

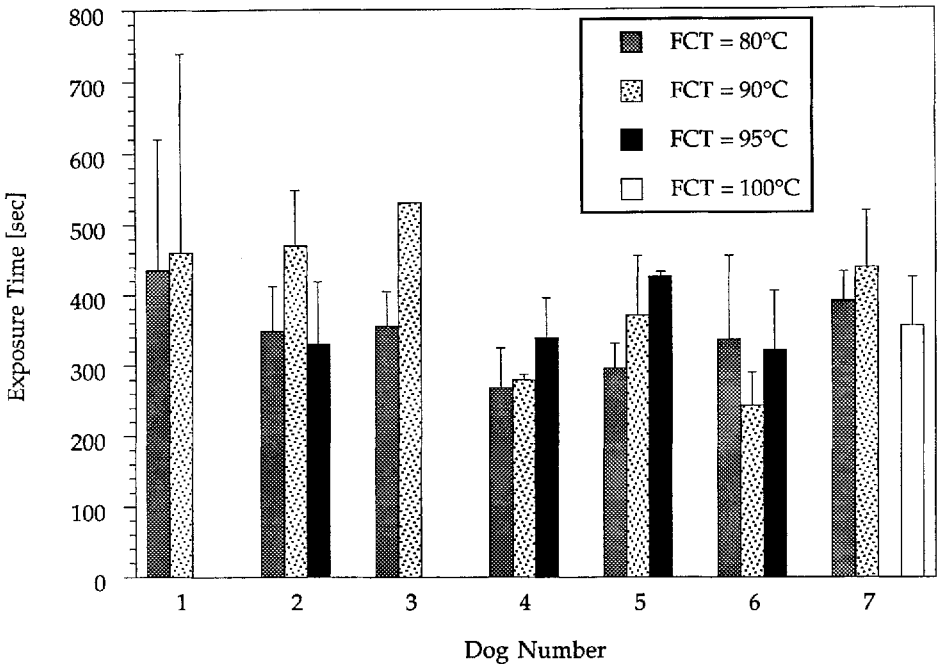

Fig. 2. "Exposure times" for argon laser-assisted intestinal welds in vitro (shown as average ± standard deviation). Laser irradiance was 22–35 W/cm^2. Two to five welds were created at each feedback control temperature (FCT) for each dog.

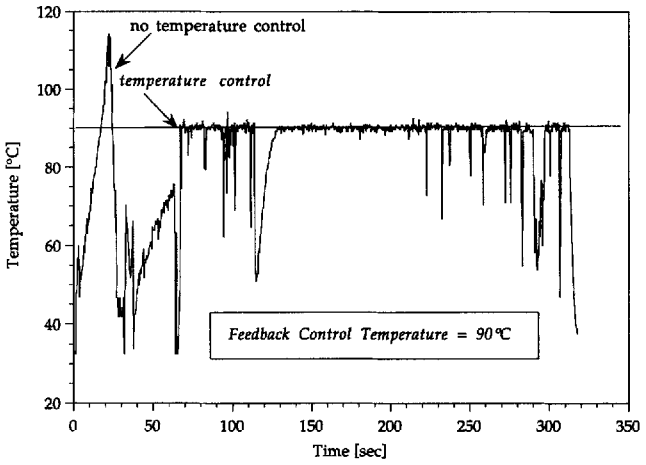

Fig. 3. Comparative temperature-time history of an intestinal welding experiment illustrating difference in temporal profiles with and without temperature feedback control. Laser irradiance was 30 W/cm^2. Note how feedback control regulates tissue surface temperature. The downward spikes in the graph are due to continuous moving of the intestinal sample within the FOV of the device.

intact tissue welds, the fusion sites were characterized by local thermal coagulation of submucosal collagen with small amounts of mucosal tissue sandwiched between the severed ends as shown in Figure 6. The surfaces exposed to the laser irradiation at all FCTs showed cell shrinkage and condensation but no carbonization or water vacuolization. At 80°C FCT there was little deep thermal alteration of the tissues, whereas at 90°, 95°, and 100°C the submucosal collagen at the severed edges was swollen and hyalinized when examined with light microscopy. The same collagens showed decreased birefringence intensity when viewed with polarizing optics (see Fig. 6). The lateral extent of submucosal thermal damage marked by partial birefringence loss was about the same for the FCTs of 90–100°C.

DISCUSSION

Early anastomotic leakage and resulting fecal peritonitis are the two important complications of gastrointestinal anastomoses carried out with sutures [27]. In contrast, laser-assisted anastomoses provide an immediate strong seal preventing early leakage and decreasing the chance of complications due to peritonitis [28–32]. Moreover, Cespanyi and associates [33] reported that laser-welded rat small intestinal anastomoses healed more rapidly with less inflammatory response and less adhesion formation compared to sutured repairs.

Intraluminal jejunum pressures in unanesthetized dogs have been reported to be ~7–8

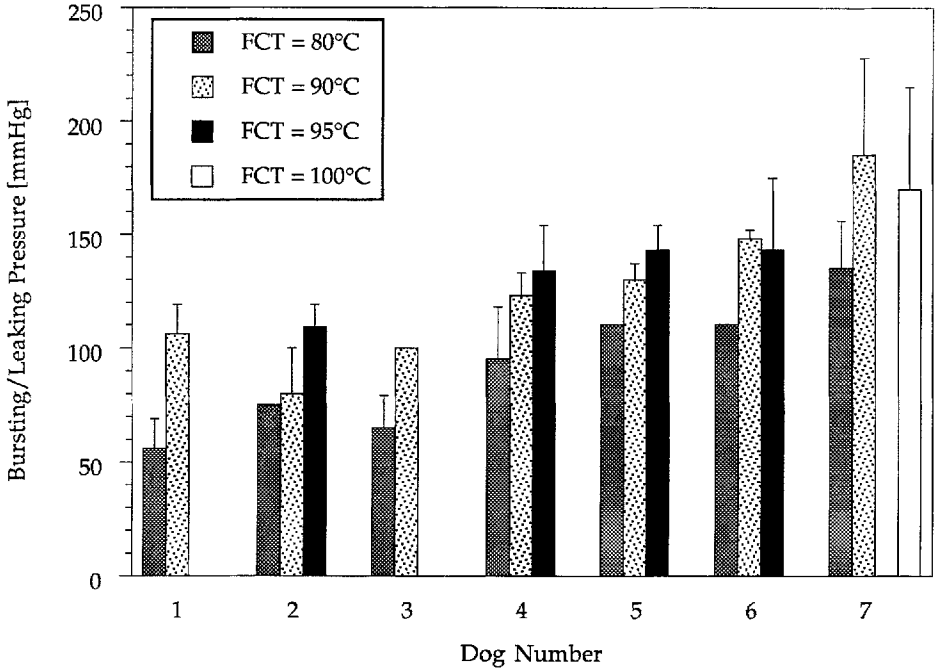

Fig. 4. Bursting/leaking pressures (BLPs) for laser-assisted intestinal welds in vitro (shown as average ± standard deviation). Laser irradiance was 22–35 W/cm^2. Two to five welds were created at each feedback control temperature (FCT) for each dog.

mmHg at rest. During peristalsis these pressures rise to as high as 30 mmHg [34]. Bursting pressures of normal canine jejunum are estimated to be well over 100 mmHg in the light of results from intact rabbit intraluminal intestinal pressures [28, 30, 31, 33]. Thus BLPs at least twice the intraluminal jejunum pressures during peristalsis, preferably over 100 mmHg, can be assumed to be a sign of good initial weld strength.

BLPs in our study varied from 50 to 225 mmHg and were directly proportional to FCT. Weaker welds were created at 80°C FCT, whereas stronger welds were created at 90°C and 95°C FCTs. There was a statistically significant increase in BLPs when FCT was raised from 80°C to 90–95°C. There was no evidence that 100°C FCT was better than 90–95°C. However, the number of experiments was too small to allow reliable comparison. Theoretically, welds created at 90–95°C had reaction rates at least a decade slower than the reaction rate at 100°C [35]. During single spot irradiation of jejunal segments, the duty cycle of laser irradiation at 95°C and 100°C was similar at 70–75%. Consequently, we expected to observe significantly lower "total exposure times" at 100°C FCT. However, the endpoint was more difficult to detect at 100°C FCT than at lower temperatures, and the samples were probably overexposed. Therefore, we postulate that welds created at temperatures below water boiling temperature are more desirable. FCTs less than 100°C may also prevent tissue from excessive surface thermal damage and desiccation resulting from water boiling in the outer layers of tissue. We also believe that FCTs less than 80°C will not produce welds strong enough to withstand normal intraluminal pressures because subsurface temperatures will be smaller than the surface temperature due to the temperature gradients within the gut wall. Hence, weld strength may be related to FCTs and the temperature gradients within the gut wall. Rastegar and associates [36] showed that axial temperature gradients during laser irradiation could be as large as 40–50°C within the first 1–2 mm in myocardium when a flat beam profile was chosen for photon propagation simulation. Springer and associates [25] found a 40–60°C temperature difference between the adventitia and intima of human saphenous vein segments during argon laser-assisted feedback controlled anastomosis at 120°C FCT [25]. Since the dog intestinal wall is ~2–3 mm thick, an intestinal weld created with the FCT set at 50–70°C could be a very weak superficial weld, because most of the thermal energy would be deposited on the surface layers of tissue and not penetrate deeply to

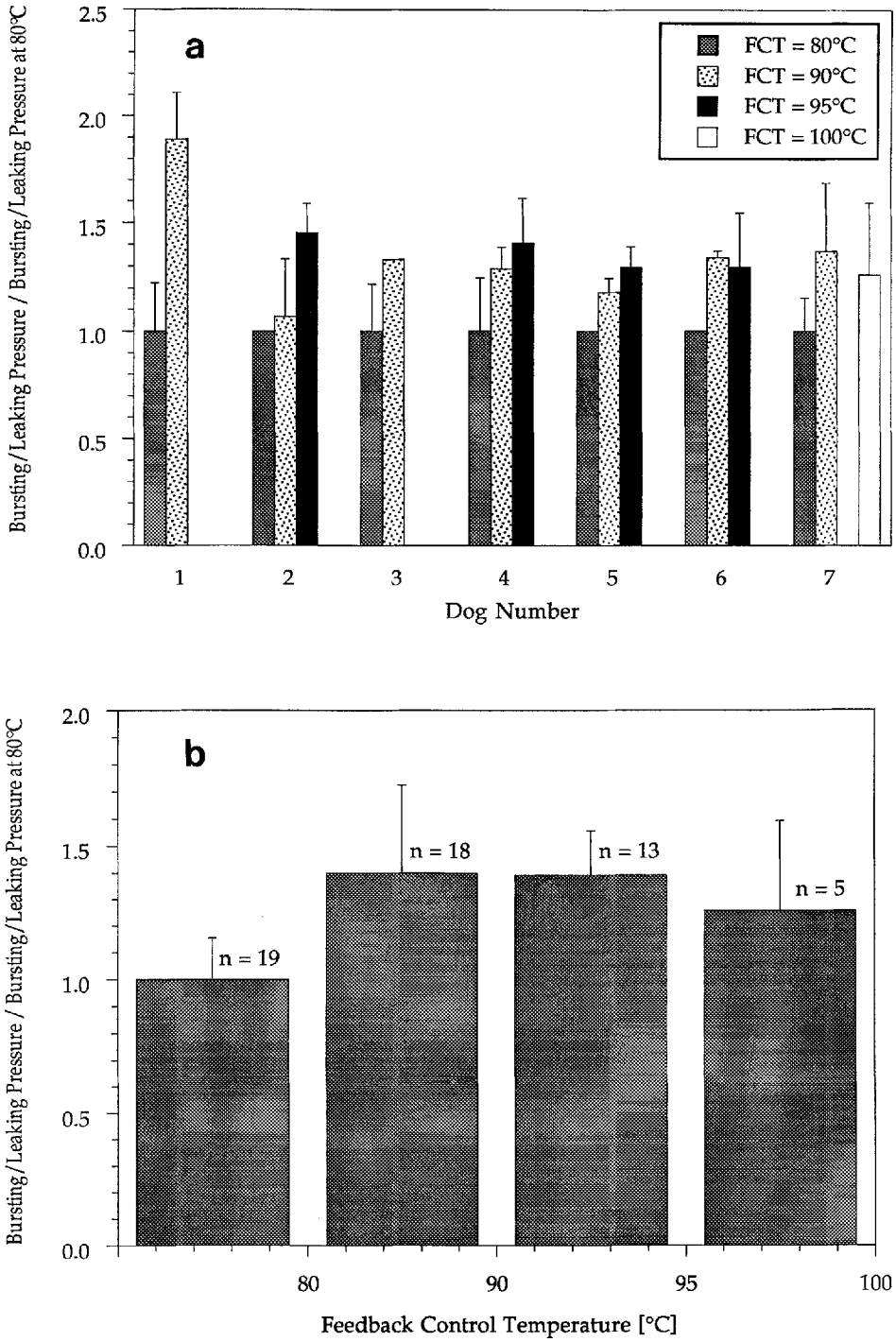

Fig. 5. (**a**) Bursting/leaking pressures (BLPs) for each dog normalized with respect to each animal's average bursting/leaking pressure at 80°C feedback control temperature (FCT) for laser-assisted intestinal welds in vitro (shown as average ± standard deviation). Laser irradiance was 22–35 W/cm^2. Two to five welds were created at each FCT for each dog. (**b**) Feedback control temperature (FCT) dependence of bursting/leaking pressures (BLPs) normalized with respect to each animal's average BLP at 80°C FCT for all laser-assisted intestinal welds in vitro (shown as average ± standard deviation). Laser irradiance was 22–35 W/cm^2. Two to five welds were created at each FCT for each dog. The BLPs of welds created 85°C and 90°C FCT were significantly different than the welds created at 80°C FCT.

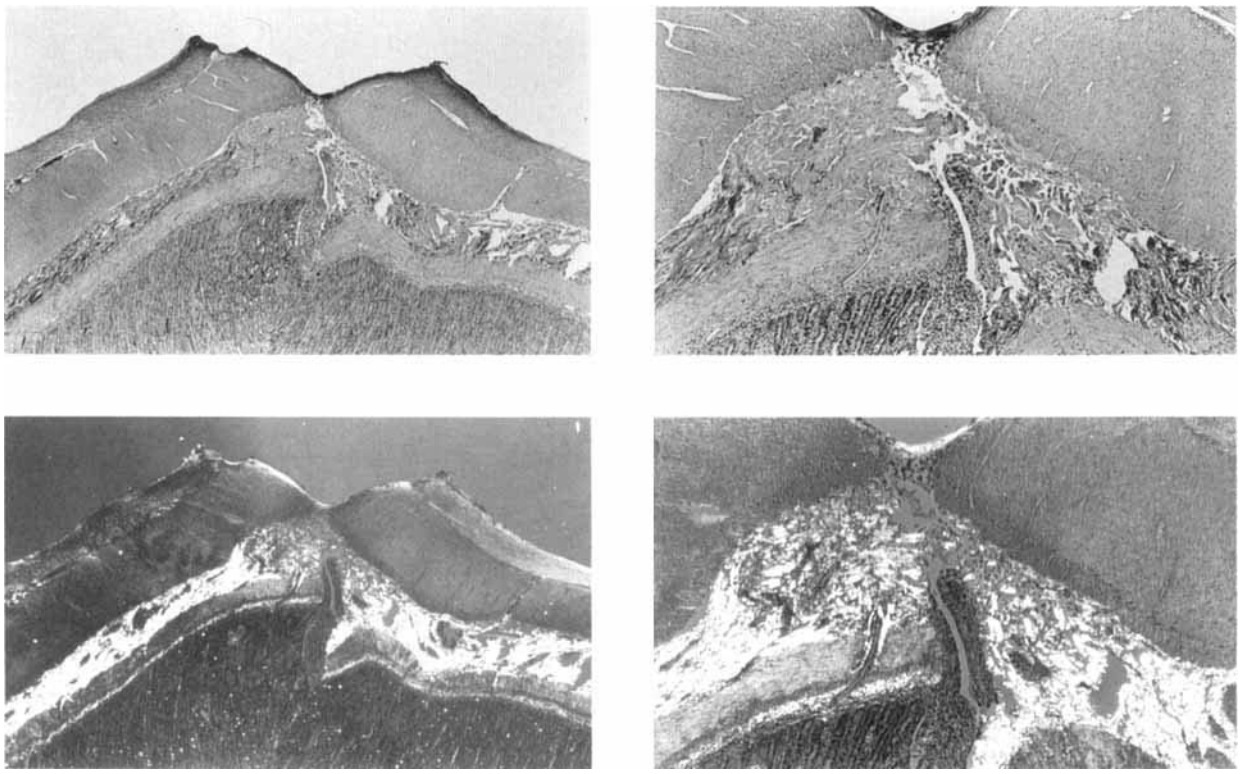

Fig. 6. H&E stained 90°C thermal feedback-controlled intestinal weld section as seen under light and polarizing light microscopy. Upper left: intact cross section of laser-assisted weld, original magnification = 10×; lower left: same anastomosis as seen with polarizing optics, note decreased birefringence of the submucosa about the irradiation site; upper right: same anastomosis, original magnification = 20×; lower right: same anastomosis as seen with polarizing optics, note decreased birefringence intensity about the irradiation site and thermal alteration of submucosal collagen, original magnification = 20×.

allow fusion of the subcutaneous collagen and mucosa that seem to form the bonds in our welds.

Histologic analysis of the edges of the broken and intact portions of the welds showed that relatively little deep thermal change was seen in tissues exposed to the 80°C FCT irradiation conditions. Those tissues subjected to 90°, 95° and 100°C conditions had stronger welds on average with more thermal alteration seen in the submucosal collagens. The observation that the lateral extent of the thermal damage was about the same for all three FCTs may be related to the use of the same end point for determination of completion of the weld during the procedure, that is, whitening of the surface. This was a study designed to compare welding success to preset control temperatures based on bursting/leaking pressures of welded tissue. Therefore, the histopathological analysis of these specimens reveals little about the mechanism of the successful laser-assisted intestinal weld. Still, the results suggest that the important site of fusion is at the submucosa with the variable participation of the mucosal tissues that may act as a solder. Similar observations were made by Vlasak and associates in rabbit gastrointestinal anastomoses [32,37].

We realize that exposure times as long as a few hundred seconds are not comparable to stapling times in intestinal surgery. Yet, our in vitro study was directed toward establishing a temperature window for successful acute intestinal welds with minimal thermal damage and acceptable initial weld strength, rather than devising a new technique for intestinal surgery. We found out that welds at 90–95°C FCT have significantly higher bursting pressures than welds created at 80°C. Although our temperature range was limited to 80–100°C, our study showed that controlled temperature tissue fusion is a feasible technique. Furthermore our study implied that dosimetry can be controlled using temperature feedback, thus avoiding excessive irradiation of the wound site that can cause unwanted desiccation and charring of tissue.

CONCLUSIONS

Dosimetry control via thermal feedback from a calibrated infrared sensor is feasible for laser-assisted tissue fusion. Laser-assisted intestinal anastomoses created in vitro using such feedback are optimally strong at 90–95°C feedback control temperatures.

ACKNOWLEDGMENTS

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